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(54) **Erythromycin A derivatives and method for preparing the same.**

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Description

The present invention relates to erythromycin A derivatives and methods for their preparation.

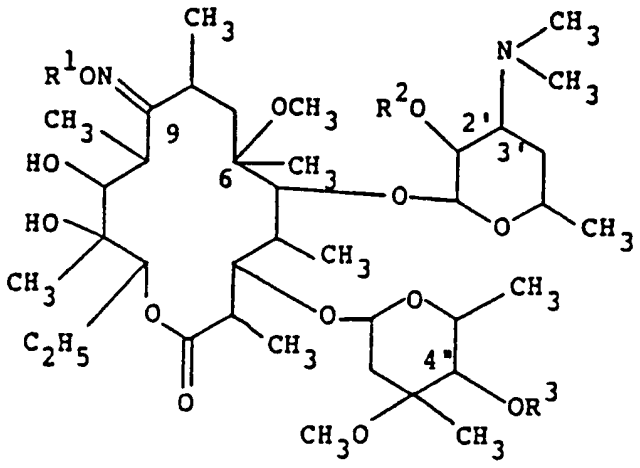
6-O-Methylerythromycins are useful as antibacterial agents or intermediates for synthesis of antibacterial agents. For example, 6-O-methylerythromycin A is not only stable under acidic conditions but also has a strong antibacterial activity when compared with erythromycin A. In particular, this compound shows excellent efficacy in the treatment of infections by oral administration, and is therefore a useful antibacterial agent.

Some methods for methylating the hydroxy group at the 6-position of the erythromycin A derivatives are known, for example, (1) a method which comprises substituting the hydrogen atom of the hydroxy group at the 2'-position and the methyl group of the dimethylamino group at the 3'-position of the erythromycin A derivatives by benzyloxycarbonyl groups, and then methylating the resulting compound (US-A-4331803), and (2) a method which comprises converting erythromycin A derivatives having a protected hydroxy group at the 2'-position and/or a protected dimethylamino group at the 3'-position into various kinds of substituted oxime derivatives, and then methylating the substituted derivatives (EP-A-0158467).

However, since erythromycin A has many hydroxy groups, then by method (1) above various kinds of erythromycin A derivatives are obtained as by-products which have methylated hydroxy groups at positions other than the 6-position. Accordingly, this method requires a complicated procedure for purification of the 6-O-methylerythromycin A derivatives, and has the drawback of providing only a low yield of the desired derivative. Although it is possible to methylate selectively the 6-hydroxy group by the method (2), when an erythromycin A 9-oxime derivative whose 2'-hydroxy group only is protected is methylated, the 3'-dimethylamino group is changed to a methyl quaternary salt under ordinary methylation conditions. Furthermore it is difficult to return the salt to a dimethylamino group. Accordingly, it is necessary to protect both of the 2'-hydroxy group and 3'-dimethylamino group in a preparative method useful in practice.

As a result of various investigations in an attempt to avoid the drawbacks of the above known methods, we have found that erythromycin A derivative whose 2'-hydroxy group is protected with substituted silyl groups is not quaternarized at the adjacent 3'-dimethylamino group even under ordinary methylation conditons.

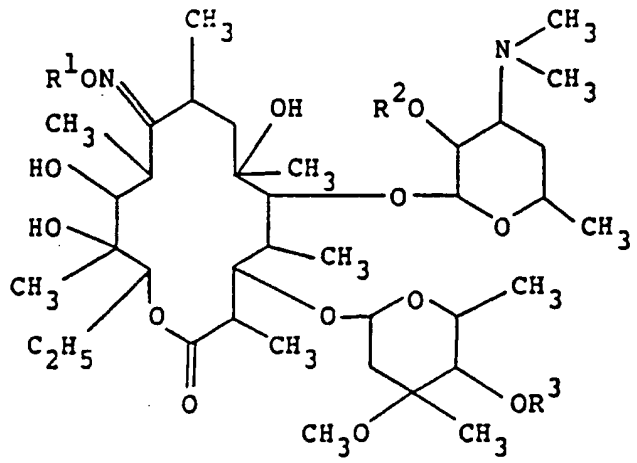
The present invention provides a 6-O-methylerythromycin A derivative represented by the general formula



I

wherein R^1 is a 2-alkenyl group having 3 to 15 carbon atoms, an arylmethyl group, or an arylmethyl group substituted by 1, 2 or 3 radicals each, independently of one another, selected from a halogen atoms, an alkoxy group having 1 to 4 carbon atoms, a nitro group and an alkoxycarbonyl group having 2 to 6 carbon atoms, R^2 is a substituted silyl group of the formula - $SiR^4R^5R^6$ (wherein R^4, R^5 and R^6 are the same as or different from one another, and each is a hydrogen atom, an alkyl group having 1 to 15 carbon atoms, a phenyl substituted alkyl group in which the alkyl moiety has 1 to 3 carbon atoms, a phenyl group, a cycloalkyl group having 5 to 7 carbon atoms or an alkenyl group having 2 to 5 carbon atoms, with the proviso that at least one of R^4, R^5 and R^6 is other than a hydrogen atom) and R^3 is a hydrogen atom or R^2.

According to another aspect, the present invention also provides an erythromycin A derivative represented by the general formula



II

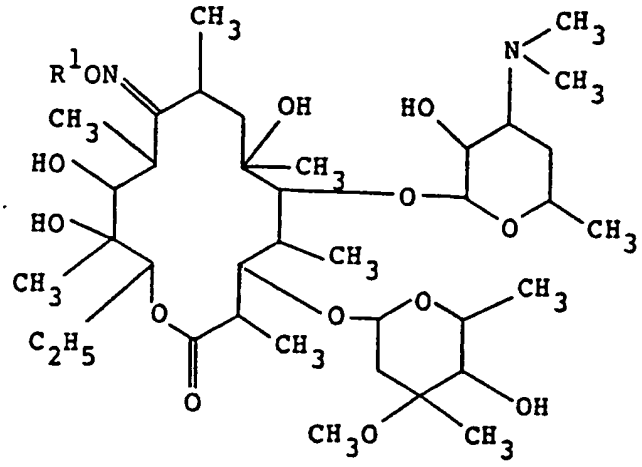
wherein R^1, R^2 and R^3 are as defined above.

According to still another aspect, the present invention provides a method for preparing a 6-O-methylerythromycin A derivative of the formula I which comprises reacting, in any desired sequence, erythromycin A 9-oxime with a compound of formula R^1-X (wherein R^1 is as defined above, and X is a halogen atom) and with a substituted silylating agent having a group R^2 to give a compound of formula II, and then reacting the compound of formula II with a methylating agent.

In this specification, the terms "alkyl", "alkoxy" and "alkenyl" used alone or in combination with another moiety mean those groups or moieties whose carbon chain may be linear or branched. The "arylmethyl group" is a benzyl group, a benzhydryl group, a trityl group or a naphthyl-methyl group. Examples of the substituted arylmethyl group are a p-methoxybenzyl group, a p-chlorobenzyl group, a m-chlorobenzyl group, an o-chlorobenzyl group, a 2,4-dichlorobenzyl group, a p-bromobenzyl group, a m-nitrobenzyl group and a p-nitrobenzyl group. Examples of the 2-alkenyl group for R^1 are an allyl group, a methallyl group, a crotyl group, a 3-methyl-2-butenyl group, a 2-pentenyl group, a 2-ethyl-2-butenyl group, a geranyl group and a neryl group. The term "halogen atom" refers, for example, to a chlorine, a bromine or iodine atom. Examples of the substituted silyl group are a trimethylsilyl group, a triethylsilyl group, an isopropyldimethylsilyl group, a tert-butyldimethylsilyl group, a (triphenylmethyl)dimethylsilyl group, a tert-butyldiphenylsilyl group, a diphenylmethylsilyl group, a diphenylvinylsilyl group, a methyldiisopropylsilyl group, a tribenzylsilyl group, a tri(p-methylphenylmethyl)silyl group, a triphenylsilyl group, a diphenylsilyl group and a dimethyloctadecylsilyl group.

Methods embodying the present invention are illustrated below in more detail.

In a first step, etherification of erythromycin A 9-oxime with a compound of formula R^1-X is carried out according to a method known per se, for example, the method described in EP-A-0158467 to give a compound of formula



III

wherein R^1 is as defined above.

The reaction of the compound of formula III with the silylating agent is carried out in a solvent in the presence of a base at 0 °C to the reflux temperature of the solvent, preferably at room temperature with stirring. Examples of the silylating agent used are chlorosilanes such as trimethylchlorosilane and tert-butyldimethychlorosilane; silylamines such as 1,1,1,3,3,3-hexamethyldisilazane, trimethylsilylimidazole and dimethylaminotrimethylsilane; bis(trimethylsilyl)acetamide, trimethylsilyldiphenylurea and bis(trimethylsilyl)-urea. The amount of the silylating agent used is 1 to 10 equivalents, preferably 1 to 5 equivalents relative to the compound of formula III.

Examples of the solvent used in the reaction are acetone, tetrahydrofuran, N,N-dimethylformamide, dimethyl sulfoxide, dioxane, 1,2-dimethoxyethane, dichloromethane and chloroform. Examples of the base are inorganic bases such as sodium hydroxide, potassium hydroxide, potassium carbonate, sodium bicarbonate and potassium bicarbonate; and organic bases such as trimethylamine, triethylamine, pyridine, 1,8-diazabicyclo[5,4,0]unde-7-cene and imidazole.

Whether silylation takes place at the 2-position only or at both of the 2'- and 4"-positions of the compound of formula III depends on the reaction conditions. However, it is preferable to use a chlorosilane for silylation at the 2-position only, and it is preferable to use both a chlorosilane and a silylamine or 1,1,1,3,3,3-hexamethyldisilazane for silylation at both the 2'- and 4"-positions.

Alternatively, the compound of formula II can be obtained by etherification after silylation of erythromycin A 9-oxime. Namely, erythromycin A 9-oxime is reacted with the silylating agent under the same silylation conditions as described above, and then the resulting compound is reacted with a compound of formula R^1-X under the same etherification conditions as described above to give the compound of formula II.

The reaction of the compound of formula II with the methylating agent for preparing the compound I can be carried out in a solvent in the presence of a base at -15 °C to room temperature, preferably at 0 °C to room temperature with stirring. Examples of the methylating agent are methyl bromide, methyl iodide, dimethyl sulfate, methyl p-toluenesulfonate and methyl methanesulfonate. It is sufficient to use 1 - 3 molar equivalents of the methylating agent relative to the compound of formula II. Examples of the solvents used are polar aprotic solvent such as N,N-dimethylformamide, dimethyl sulfoxide, N-methyl-2-pyrrolidone, hexamethylphosphoric triamide, a mixture thereof or a mixture of one of these solvents and a solvent such as tetrahydrofuran, 1,2-dimethoxyethane, acetonitrile or ethyl acetate. Examples of the base are sodium hydroxide, potassium hydroxide, sodium hydride, potassium t-butoxide and potassium hydride. The amount of the base used is usually 1 - 2 molar equivalents relative to the compound of formula II.

In order to prevent the quaternarization of the 3'-dimethylamino group when the compound of formula II is methylated, it is essential to protect the 2'-hydroxy group with the substituted silyl ether, but not necessarily essential to etherify the 4"-hydroxy group with the substituted silyl group.

The compound of formula II may be used after isolation or without isolation for reacting with the methylating agent.

Erythromycin A 9-oxime derivatives of the present invention exist in two isomeric forms (syn- and anti-forms). For the purpose of the present invention, these compounds may exist in either of these isomeric

forms or in a mixture thereof.

In the method for preparing the 6-O-methylerythromycin A derivatives of the present invention, it is not necessary to protect the 3'-dimethylamino group; hence, neither is not necessary to carry out the 3'-N-methylation.

The methylation of the hydroxy group at the 6-position in a method of the present invention is as highly selective as the prior art method. Furthermore, the substituted silyl groups used for the protection of the hydroxy groups at the 2'- and 4"-positions can be easily eliminated.

Therefore, the present invention can provide 6-O-methylerythromycin A in high yield and economically. Namely, the compound of formula I can be connected to 6-O-methylerythromycin A, for example, by the following method.

The elimination of the substituted silyl groups (R^2 and R^3) at the 2'- and 4"-positions of the compound of formula I can be carried out easily by treatment with an acid (e.g., formic acid) in an alcohol or with tetrabutyl ammoniumfluoride in tetrahydrofuran.

The elimination of R^1 group of the resulting compound can be carried out by homogeneous or heterogeneous hydrogenolysis known per se. For example, this reaction may be carried out in an alcoholic solvent (e.g., methanol or ethanol) in the presence of a catalyst such as palladium black or palladium carbon under a hydrogen atmosphere with stirring. The addition of, for example, formic acid or acetic acid is convenient for the progress of the reaction.

This reaction can also be carried out easily in the presence of a suitable hydrogen source (e.g., ammonium formate, sodium formate, and a mixture of these formates and formic acid) and a catalyst (e.g., palladium carbon or palladium black) in an organic solvent (e.g., methanol, ethanol or N,N-dimethylformamide) with stirring at room temperature to 70 °C.

Furthermore, this reaction may be carried out by using a platinum containing compound and a ligand as a catalyst. Examples of the platinum containing compound are the salts or complexes of ruthenium, rhodium, palladium and platinum, and examples of the ligand are phosphor compounds such as triphenylphosphine, tri-n-butylphosphine, triethylphosphite and 1,2-ethylene(diphenyl)phosphine. Usually, a mixture of palladium acetate and triphenylphosphine is used. This reaction can be carried out in the presence of formic acid or a salt thereof. Examples of the salt of formic acid are ammonium salts thereof such as ammonium formate, trimethylammonium formate and triethylammonium formate, and alkali metal salts thereof such as sodium formate and potassium formate.

The procedure for elimination of R^2 and R^3 and that of R^1 may be carried out in the reverse order without any trouble.

6-O-Methylerythromycin A 9-oxime thus obtained can be converted easily to 6-O-methylerythromycin A by deoximation using, for example, sodium hydrogen sulfite, titanium trichloride-ammonium acetate, sodium nitrite-hydrochloric acid or sodium hydrosulfite ($Na_2S_2O_4$).

The present invention will now be illustrated in more detail by Examples which show the method for preparing the compound of formula I and Referential Examples which show the method for preparing 6-O-methylerythromycin A.

Example 1

Preparation of 2'-O-trimethylsilylerythromycin A 9-(O-benzyloxime)

To a solution of 3.36 g of erythromycin A 9-(O-benzyloxime) and 0.7 ml of triethylamine in 30 ml of N,N-dimethylformamide was added dropwise at room temperature 0.7 ml of trimethylchlorosilane, and the mixture was stirred for 10 minutes. To the reaction solution was added isopropyl ether, and the mixture was washed with, in turn, water and a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was evaporated and the resulting crude product was recrystallized from isopropyl ether to give 1.35 g of the title compound as colorless needles.

m.p. 104 - 106 °C

Mass(FAB); m/z : 911(MH^+)

PMR($CDCl_3$)

δ (ppm) = 0.11(2'-O-TMS), 2.23[3'N$(CH_3)_2$], 3.33(3"-OCH_3)

CMR($CDCl_3$)

δ (ppm) = 1.0(2'-O-TMS), 41.0[3'-N$(CH_3)_2$], 49.5(3"-OCH_3)

(TMS as used above and hereinafter is a trimethylsilyl group)

Example 2

Preparation of 2',4"-O-bis(trimethylsilyl)erythromycin A 9-(O-benzyloxime)

To a solution of 2.24 g of trimethylsilylimidazole and 1.74 g of trimethylchlorosilane in 20 ml of dry dichloromethane was added at once at room temperature a solution of 6.72 g of erythromycin A 9-(O-benzyloxime) in 40 ml of dichloromethane, and the mixture was stirred at room temperature for 10 minutes. Chloroform was added, and the mixture was washed with, in turn, water and a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was evaporated and the resulting crude product was recrystallized from acetone-water to give 5.27 g of the title compound as colorless needles.

m.p. 97 - 100 °C

Mass(FAB); m/z : 983(MH^+)

PMR($CDCl_3$)

δ (ppm) = 0.09(2'-O-TMS), 0.15(4"-O-TMS), 2.22[3'-N(CH_3)$_2$], 3.31(3"-OCH_3)

CMR($CDCl_3$);

δ (ppm) = 0.9(4"-O-TMS), 1.0(2'-O-TMS), 41.0[3'-N(CH_3)$_2$], 49.7(3"-OCH_3)

Example 3

Preparation of 2'-O-trimethylsilyl-6-O-methylerythromycin A 9-(O-benzyloxime)

To a solution of 2.28 g of 2'-O-trimethylsilylerythromycin A 9-(O-benzyloxime) in 20 ml of a mixture of dimethyl sulfoxide and tetrahydrofuran (1 : 1) were added 0.38 ml methyl iodide and 280 mg of 85% potassium hydroxide powder, and the mixture was stirred at room temperature for 2 hours. To the reaction solution was added ethyl acetate, and the mixture was washed with, in turn, water and a saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was evaporated to give 2.32 g of the glassy title compound.

Mass(FAB); m/z : 925(MH^+)

PMR($CDCl_3$)

δ (ppm) = 0.09(2'-O-TMS), 2.23[3'-N(CH_3)$_2$], 3.03(6-OCH_3), 3.34(3"-OCH_3)

Example 4

Preparation of 2',4"-O-bis(trimethylsilyl)-6-O-methylerythromycin A 9-(O-benzyloxime)

By treating 3.93 g of 2',4"-O-bis(trimethylsilyl)erythromycin A 9-(O-benzyloxime) according to a procedure similar to that of Example 3, there was obtained 3.89 g of the glassy title compound.

m.p. 115 - 116 °C (recrystallized from methanol)

Mass(FAB); m/z : 997(MH^+)

PMR($CDCl_3$)

δ (ppm) = 0.09(2'-O-TMS), 0.15(4"-O-TMS), 2.21[3'-N(CH_3)$_2$], 3.03(6-OCH_3), 3.32(3"-OCH_3)

CMR($CDCl_3$)

δ (ppm) = 0.9(4"-O-TMS), 1.1(2'-OCH_3), 41.0[3'-N(CH_3)$_2$], 49.7(3"-OCH_3), 50.7(6-OCH_3)

Example 5

Preparation of 2'-O-trimethylsilylerythromycin A 9-(O-allyloxime)

By treating 1 g of erythromycin A 9-(O-allyloxime) according to a procedure similar to that of Example 1, there was obtained the crude product, which was then purified by alumina column chromatography (eluent; acetone/ n-hexane = 1/10 - 1/5) to give 0.35 g of the glassy title compound.

m.p. 93 - 96 °C (recrystallized from n-hexane)

Mass(EI); m/z : 860(M^+)

PMR($CDCl_3$)

δ (ppm) = 0.11(2'-O-TMS), 2.23[3'-N(CH_3)$_2$], 3.32(3"-OCH_3)

CMR($CDCl_3$)

δ (ppm) = 1.0(2'-O-TMS), 41.0[3'-N(CH_3)$_2$], 49.5(3"-OCH_3)

Example 6

Preparation of 2',4"-O-bis(trimethylsilyl)erythromycin A 9-(O-allyloxime)

1 g of erythromycin A 9-(O-allyloxime) was allowed to react according to a procedure similar to that of Example 2, and then 100 ml of n-hexane was added to the reaction solution. The insoluble was filtered off, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (eluent; acetone/ n-hexane/triethylamine = 1/10/0.1) to give 0.70 g of the glassy title compound.

m.p. 85 - 89 °C (recrystallized from acetone)
Mass(EI); m/z : 932(M^+)
PMR($CDCl_3$)
δ (ppm) = 0.10(2'-O-TMS), 0.14(4"-O-TMS), 2.22[3'-N(CH_3)$_2$], 3.31(3"-OCH_3)

Example 7

Preparation of 2'-O-trimethylsilyl-6-O-methylerythromycin A 9-(O-allyloxime)

To a solution of 4 g of erythromycin A 9-(O-allyloxime) and 1.4 ml of triethylamine in 20 ml of N,N-dimethylformamide was added dropwise at room temperature 1.35 ml of trimethylchlorosilane, and the mixture was stirred for 20 minutes. 100 ml of water was added, and the mixture was extracted with ethyl ether. The organic layer was washed with a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was evaporated to give 3.86 g of the crude product of 2'-O-trimethylsilylerythromycin A 9-(O-allyloxime).

To a solution of the above compound in 30 ml of a mixture of dimethyl sulfoxide and tetrahydrofuran (1 : 1), were added under ice-cooling 0.42 ml of methyl iodide and then 357 mg of 85% sodium hydroxide powder, and the mixture was stirred for 1.5 hours. After completion of the reaction, 0.5 ml of 50% aqueous dimethylamine solution was added, and the mixture was stirred for an hour. 100 ml of water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was evaporated, and the residue was purified by silica gel column chromatography (eluent; acetone/n-hexane/triethylamine = 1/5/0.1) to give 1.45 g of the glassy title compound.

m.p. 155 - 158 °C (recrystallized from n-hexane)
Mass(EI); m/z : 874(M^+)
PMR($CDCl_3$)
δ (ppm) = 0.10(2'-O-TMS), 2.22[3'-N(CH_3)$_2$], 3.08(6-OCH_3), 3.33(3"-OCH_3)
CMR($CDCl_3$)
δ (ppm) = 1.1(2'-O-TMS), 41.0[3'-N(CH_3)$_2$], 49.4(3"-OCH_3), 50.9(6-OCH_3)

Example 8

Preparation of 2',4"-O-bis(trimethylsily)-6-O-methylerythromycin A 9-(O-allyloxime)

To a solution of 3.51 ml of trimethylsilylimidazole and 3.04 ml of trimethylchlorosilane in 25 ml of dry dichloromethane was added at once at room temperature a solution of 9.5 g of erythromycin A 9-(O-allyloxime) in 125 ml of dichloromethane, and the mixture was stirred at room temperature for 10 minutes. To the reaction solution was added 400 ml of n-hexane, the insoluble material was filtered off, and the filtrate was concentrated. To the residue was added 200 ml of n-hexane, the resulting insoluble material was filtered off, and the filtrate was concentrated. To a solution of the residue in 75 ml of a mixture of dimethyl sulfoxide and tetrahydrofuran (1 : 1) were added under ice-cooling 1 ml of methyl iodide and then 854 mg of 85% potassium hydroxide powder, and the mixture was stirred for 1.5 hours. After completion of the reaction, a treatment similar to that of Example 7 gave 10.2 g of the title compound.

m.p. 96 - 101 °C (recrystallized from acetone-water)
Mass(EI); m/z : 946(M^+)
PMR($CDCl_3$)
δ (ppm) = 0.09(2'-O-TMS), 0.15(4"-O-TMS), 2.22[3'-N(CH_3)$_2$], 3.09(6-OCH_3), 3.32(3"-OCH_3)
CMR($CDCl_3$)
δ (ppm) = 0.9(6-O-TMS), 1.1(2'-O-TMS), 41.0[3'-N(CH_3)$_2$], 49.7(3"-OCH_3), 50.9(6-OCH_3)

Example 9

Preparation of 2',4"-O-bis(trimethylsilyl)-6-O-methylerythromycin A 9-(O-allyloxime) from erythromycin A 9-oxime

To a solution of 10 g of erythromycin A 9-oxime in 75 ml of tetrahydrofuran were added 1.25 ml of allyl bromide and 970 mg of 85% potassium hydroxide powder, and the mixture was stirred at room temperature for 2 hours. To the reaction solution was added 1 ml of 50% aqueous dimethylamine solution, and the mixture was stirred for 30 minutes, poured into a mixture of methanol and water (50 ml : 200 ml) and stirred under ice-cooling for 30 minutes. The resulting precipitate was collected by filtration, washed with water, dissolved in chloroform and dried over anhydrous magnesium sulfate. The solvent was evaporated to give 9.7 g of crude erythromycin A 9-(O-allyloxime).

To a solution of 3.58 ml of trimethylsilylimidazole and 3.10 ml of trimethylchlorosilane in 25 ml of dry dichloromethane was added at once at room temperature a solution of 9.7 g of erythromycin A 9-(O-allyloxime), obtained above, in 125 ml of dichloromethane, and the mixture was stirred at room temperature for 10 minutes. To the reaction solution was added 200 ml of n-hexane, the resulting insoluble material was filtered off, and the filtrate was concentrated. To the residue was added once more 200 ml of n-hexane, the insoluble material was filtered off, and the filtrate was concentrated to give 10 g of crude 2',4"-O-bis-(trimethylsilyl)erythromycin A 9-(O-allyloxime).

To a solution of 10 g of crude 2',4"-O-bis(trimethylsilyl)erythromycin A 9-(O-allyloxime), obtained above, in 75 ml of a mixture of dimethyl sulfoxide and tetrahydrofuran (1 : 1) were added 1 ml of methyl iodide and then 837 mg of 85% potassium hydroxide powder, and the mixture was stirred under ice-cooling for 1.5 hours. After completion of the reaction, 1 ml of 50% aqueous dimethylamine solution was added, and the mixture was stirred at room temperature for an hour. 200 ml of water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution and then dried over anhydrous magnesium sulfate. The solvent was evaporated to give 10.3 g of crude 2',4"-O-bis(trimethylsilyl)-6-O-methylerythromycin A 9-(O-allyloxime). Purification similar to that of Example 8 gave the title compound, which was identical with the compound obtained in Example 8 in terms of melting point, and spectra of mass, PMR and CMR.

Example 10

Preparation of 2',4"-O-bis(trimethylsilyl)erythromycin A 9-(O-benzyloxime) from erythromycin A 9-oxime

To a solution of 3.79 g of erythromycin 9-oxime and 0.75 ml of benzyl chloride in 30 ml of N,N-dimethylformamide was added under ice-cooling 0.24 g of sodium hydride (60%). After stirring for 2 hours, 2.5 ml of 1,1,1,3,3,3-hexamethyldisilazane and 0.99 g of pyridine hydrochloride were added, and the mixture was stirred for a further 6 hours. After being allowed to stand overnight, the reaction solution was poured into water and extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated and the resulting crude product was recrystallized from an aqueous acetone to give 3.0 g of the title compound, which was identical with the compound obtained in Example 2 in terms of melting point and spectra of mass and PMR.

Example 11

Preparation of 2',4"-O-bis(trimethylsilyl)-6-O-methylerythromycin A 9-[O-(o-chlorobenzyl)oxime]

(1) To a solution of 90 g of erythromycin A 9-oxime in 500 ml of N,N-dimethylformamide were added 23.6 g of o-chlorobenzyl chloride and 9.7 g of 85% potassium hydroxide powder, and the mixture was stirred under ice-cooling for 30 minutes. After completion of the reaction, the mixture was extracted with ethyl acetate, washed with, in turn, water and a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give 98 g of erythromycin A 9-[O-(o-chlorobenzyl)oxime].

m.p. 114 - 117° C (recrystallized from n-hexane)

(2) To a solution of 8.7 g of the above compound in 80 ml of ethyl acetate was added a solution of 2.53 ml of trimethylchlorosilane and 2.8 g of trimethylsilylimidazole in 10 ml of ethyl acetate, and the mixture was stirred at room temperature for an hour. To the mixture was added n-hexane, and the mixture was washed with, in turn, water and a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was evaporated to give 9.78 g of glassy 2',4"-O-bis(trimethylsilyl)-erythromycin A 9-[O-(o-chlorobenzyl)oxime].

Mass(EI); m/z : 1016(M^+)
PMR($CDCl_3$)
δ (ppm) = 0.10(2'-O-TMS), 0.15(4"-O-TMS), 2.23[3'-N(CH_3)$_2$], 3.30(3"-OCH_3)

(3) To a solution of 5.09 g of 2',4"-O-bis(trimethylsilyl)erythromycin A 9-[O-(o-chlorobenzyl)oxime] in 100 ml of a mixture of dimethyl sulfoxide and tetrahydrofuran (1 : 1) were added 0.41 ml of methyl iodide and then 360 mg of 85% potassium hydroxide powder, and then the mixture was stirred under ice-cooling for 1.5 hours. To the reaction solution was added 2 ml of 50% aqueous dimethyl amine solution, and the stirring was continued for 30 minutes. Thereafter, to the mixture was added n-hexane, and the resulting solution was washed with, in turn, water and a saturated aqueous sodium chloride solution and dried over magnesium sulfate. The solvent was evaporated under reduced pressure to give 4.3 g of the glassy title compound.

Mass(EI); m/z : 1030(M^+)
PMR($CDCl_3$)
δ (ppm) = 0.10(2'-O-TMS), 0.15(4"-O-TMS), 2.22[3'-N(CH_3)$_2$], 3.02(6-OCH_3), 3.32(3"-OCH_3)

Example 12

Preparation of 2',4"-O-bis(trimethylsilyl)erythromycin A 9-[O-(o-chlorobenzyl)oxime] from erythromycin A 9-[O-(o-chlorobenzyl)oxime]

To a solution of 15.27 g of erythromycin A 9-[O-(o-chlorobenzyl)oxime], obtained in Example 11(1), in 150 ml of N,N-dimethylformamide were added 7.8 ml of 1,1,1,3,3,3-hexamethyldisilazane and 2.6 g of pyridine hydrochloride, and the mixture was stirred at room temperature for 3 hours. The reaction solution was poured into water and extracted with ethyl acetate, and the extract was washed with, in turn, water and a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give 14.5 g of the title compound, which was identical with the compound obtained in Example 11(2) in terms of spectra of mass and PMR.

Example 13

Preparation of 2',4"-O-bis(trimethylsilyl)erythromycin A 9-[O-(o-chlorobenzyl)oxime] from erythromycin A 9-oxime

To a solution of 3 g of erythromycin A 9-oxime in 15 ml of N,N-dimethylformamide were added 0.773 g of o-chlorobenzyl chloride and 0.192 g of 60% sodium hydride, and the mixture was stirred under ice-cooling for 2 hours. After completion of the reaction, the mixture was warmed to room temperature. To the reaction mixture were added 1.69 ml of 1,1,1,3,3,3-hexamethyldisilazane and 0.321 g of ammonium chloride, and the mixture was stirred at room temperature for 20 hours. To the reaction solution were added 50 ml of n-hexane and 100 ml of a saturated aqueous sodium chloride solution, and the organic layer was washed with a saturated aqueous sodium chloride solution (100 ml x 2) and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give 4.2 g of the title compound, which was identical with the compound obtained in Example 11(2) in terms of spectra of mass and PMR.

Referential Example 1

Preparation of 6-O-methylerythromycin A from 2',4"-O-bis(trimethylsilyl)-6-O-methylerythromycin A 9-(O-allyloxime)

To a solution of 10.3 g of crude 2',4"-O-bis(trimethylsilyl)-6-O-methylerythromycin A 9-(O-allyloxime), obtained in Example 9, in 100 ml of methanol was added 6.2 ml of 99% formic acid, and the mixture was stirred at 50°C for an hour. To the reaction solution was added 300 ml of water, and the mixture was made basic with 2N aqueous sodium hydroxide solution and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was evaporated to give 8.93 g of crude 6-O-methylerythromycin A 9-(O-allyloxime).

To a solution of 8.93 g of crude 6-O-methylerythromycin A 9-(O-allyloxime), obtained above, in a mixture of 50 ml of dioxane and 7.5 ml of water were added 89 mg of palladium acetate, 539 mg of triphenyl phosphine and 9.7 g of triethylammonium formate, and the mixture was refluxed for 30 minutes.

After completion of the reaction, the solvent was evaporated under reduced pressure, 200 ml of diethyl ether was added, and the mixture was extracted with 10% acetic acid. The acetic acid layer was washed with, in turn, diethyl ether and n-hexane, made basic with 5N-sodium hydroxide and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate, and the solvent was evaporated to give 8.5 g of crude 6-O-methyleryth-romycin A 9-oxime.

To a solution of 8.5 g of 6-O-methylerythromycin A 9-oxime, obtained above, in a mixture of 40 ml of ethanol and 40 ml of water were added 4.65 g of sodium hydrogen sulfite and 1 ml of 99% formic acid, and the mixture was refluxed for 100 minutes. To the reaction solution was added 130 ml of water, and the mixture was adjusted to pH about 9.5 with an aqueous sodium hydroxide solution and stirred under ice-cooling for an hour. The resulting precipitate was collected by filtration, washed thoroughly with water, and recrystallized from ethanol to give 4.19 g of 6-O-methylerythromycin A.

m.p. 223 - 225 °C.

Referential Example 2

Preparation of 6-O-methylerythromycin A from 2',4"-O-bis(trimethylsilyl)-6-O-methylerythromycin A 9-[O-(o-chlorobenzyl)oxime]

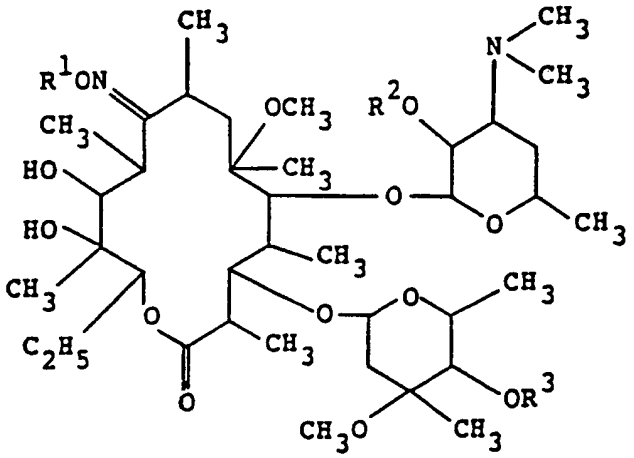
To a solution of 2.8 g of crude 2',4"-O-bis(trimethylsilyl)-6-O-methylerythromycin A 9-[O-(o-chlorobenzyl)oxime], obtained in Example 12, in 30 ml of methanol were added 450 mg of 10% palladium carbon, 1.8 ml of formic acid and 300 mg of ammonium formate, and the mixture was stirred at 60 °C for 2 hours. The palladium catalyst was filtered off, and the filtrate, after addition of 200 ml of water, was made basic with 2N aqueous sodium hydroxide solution. The precipitate which formed was collected by filtration, washed with water and dried to give 1.7 g of crude 6-O-erythromycin A 9-oxime.

By reacting 6-O-erythromycin A 9-oxime thus obtained with sodium hydrogen sulfite and 99% formic acid according to a procedure similar to that of Referential Example 1, there was obtained 1.17 g of 6-O-methylerythromycin A as crystals.

m.p. 223 - 225 °C.

Claims

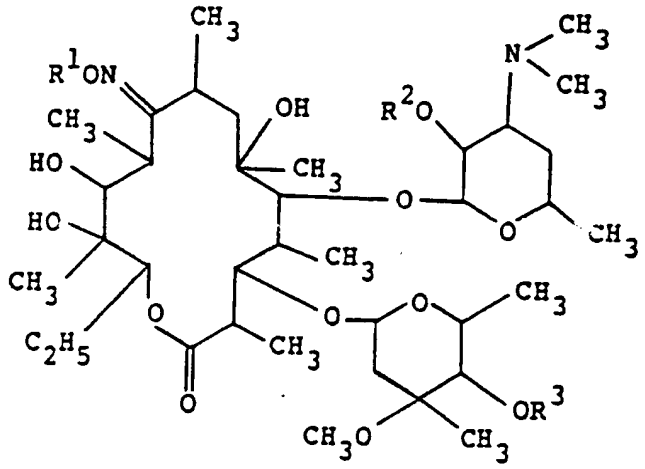
1. A 6-O-methylerythromycin A derivative represented by the general formula



wherein R^1 is a 2-alkenyl group having 3 to 15 carbon atoms, an arylmethyl group selected from benzyl, benzhydryl, trityl and naphthyl-methyl groups or a said arylmethyl group substituted by 1 to 3 members each, independently of one another, selected from a halogen atom, an alkoxy group having 1 to 4 carbon atoms, a nitro group and an alkoxycarbonyl group having 2 to 6 carbon atoms, R^2 is a substituted silyl group of the formula - $SiR^4R^5R^6$ (wherein R^4, R^5 and R^6 are the same as or different from each other, and each is a hydrogen atom, an alkyl group having 1 to 15 carbon atoms, a phenyl

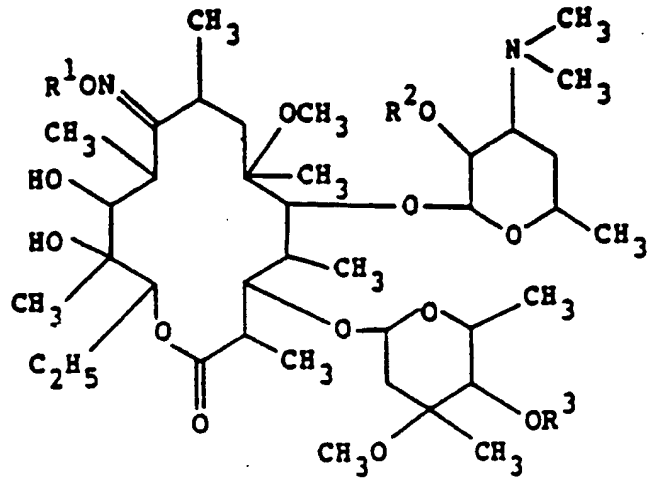
substituted alkyl group in which alkyl moiety has 1 to 3 carbon atoms, a phenyl group, a cycloalkyl group having 5 to 7 carbon atoms or an alkenyl group having 2 to 5 carbon atoms, wtih the proviso that at least one of R^4, R^5 and R^6 is other than a hydrogen atom) and R^3 is a hydrogen atom or R^2.

2. An erythromycin A derivative represented by the general formula



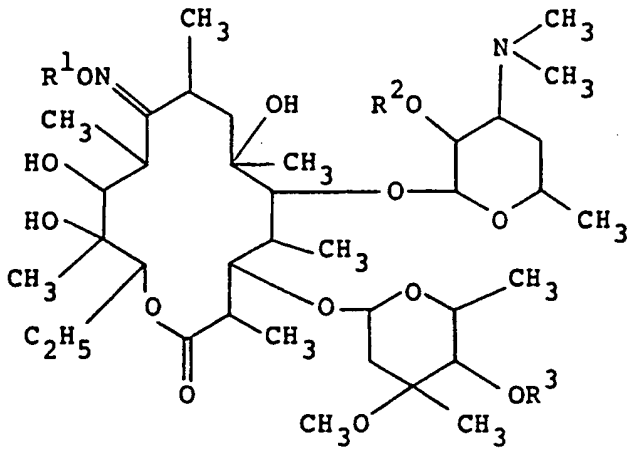
wherein R^1 is a 2-alkenyl group having 3 to 15 carbon atoms, an arylmethyl group selected from benzyl, benzhydryl, trityl and naphthyl-methyl groups or a said arylmethyl group substituted by 1 to 3 members selected from a halogen atom, an alkyl group having 1 to 4 carbon atoms, an alkoxy group having 1 to 4 carbon atoms, a nitro group and an alkoxycarbonyl group having 2 to 6 carbon atoms, R^2 is a substituted silyl group of the formula $-SiR^4R^5R^6$ (wherein R^4, R^5 and R^6 are the same as or different from each other, and each is a hydrogen atom, an alkyl group having 1 to 15 carbon atoms, a phenyl substituted alkyl group in which the alkyl moiety has 1 to 3 carbon atoms, a phenyl group, a cycloalkyl group having 5 to 7 carbon atoms or an alkenyl group having 2 to 5 carbon atoms, with the proviso that at least one of R^4, R^5 and R^6 is other than a hydrogen atom) and R^3 is a hydrogen atom or R^2.

3. A method for preparing a 6-O-methylerythromycin A derivative represented by the general formula



wherein R^1 is a 2-alkenyl group having 3 to 15 carbon atoms, an arylmethyl group selected from benzyl, benzhydryl, trityl and naphthyl-methyl groups or a said arylmethyl group substituted by 1 to 3

members each, independently of one another, selected from a halogen atom, an alkoxy group having 1 to 4 carbon atoms, a nitro group and an alkoxycarbonyl group having 2 to 6 carbon atoms, R^2 is a substituted silyl group of the formula - $SiR^4R^5R^6$ (wherein R^4, R^5 and R^6 are the same as or different from each other, and each is a hydrogen atom, an alkyl group having 1 to 15 carbon atoms, a phenyl substituted alkyl group in which the alkyl moiety has 1 to 3 carbon atoms, a phenyl group, a cycloalkyl group having 5 to 7 carbon atoms or an alkenyl group having 2 to 5 carbon atoms, with the proviso that at least one of R^4, R^5 and R^6 is other than a hydrogen atom) and R^3 is a hydrogen atom or R^2, which comprises reacting, in any desired sequence, erythromycin A 9-oxime with a compound of formula R^1-X (wherein R^1 is as defined above, and X is a halogen atom) and with a substituted silylating agent having a group R^2 to give a compound represented by the general formula



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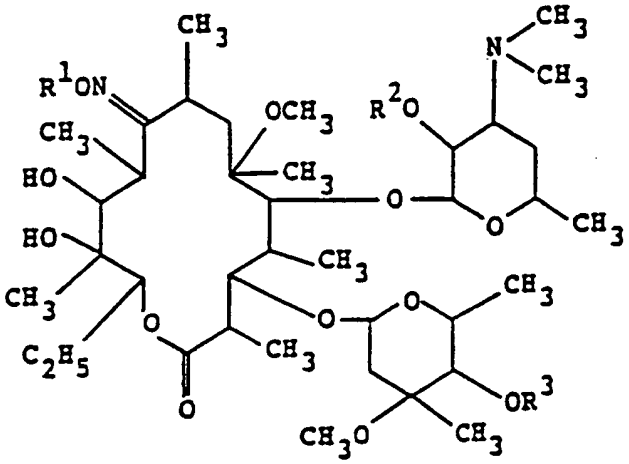
wherein R^1, R^2 and R^3 are as defined above), and then reacting the resulting compound with a methylating agent.

Patentansprüche

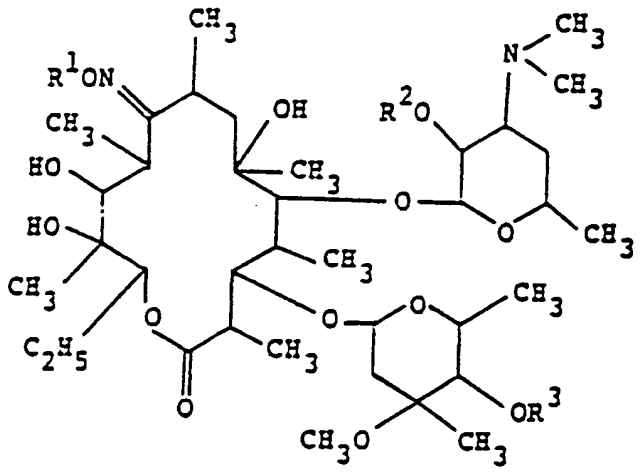
1. 6-O-Methylerythromycin A-Derivat, dargestellt durch die allgemeine Formel



wobei R^1 eine 2-Alkenylgruppe mit 3 bis 15 Kohlenstoffatomen ist, oder eine Arylmethylgruppe, ausgewählt unter Benzyl-, Benzhydryl-, Trityl- und Naphthylmethylgruppen, oder die Arylmethylgruppe, substituiert durch 1 bis 3 Vertreter, welche unabhängig voneinander unter einem Halogenatom, einer Alkoxygruppe mit 1 bis 4 Kohlenstoffatomen, einer Nitrogruppe und einer Alkoxycarbonylgruppe mit 2

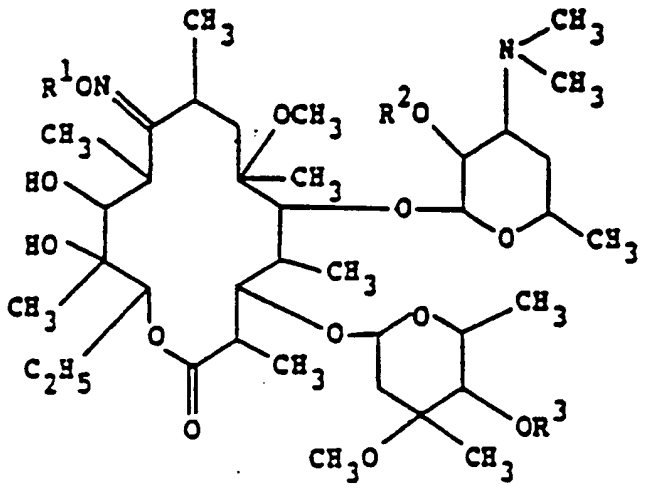
bis 6 Kohlenstoffatomen ausgewählt werden; R^2 ist eine substituierte Silylgruppe der Formel $SiR^4R^5R^6$ (wobei R^4, R^5 und R^6 gleich oder verschieden voneinander sind und jeweils ein Wasserstoffatom, eine Alkylgruppe mit 1 bis 15 Kohlenstoffatomen, eine phenylsubstituierte Alkylgruppe, in welcher die Alkyleinheit 1 bis 3 Kohlenstoffatome hat, eine Phenylgruppe, eine Cycloalkylgruppe mit 5 bis 7 Kohlenstoffatomen, oder eine Alkenylgruppe mit 2 bis 5 Kohlenstoffatomen, darstellt, wobei mindestens eines unter R^4, R^5 und R^6 verschieden von einem Wasserstoffatom ist) und R^3 stellt ein Wasserstoffatom oder R^2 dar.

2. Erythromycin A-Derivat, dargestellt durch die allgemeine Formel



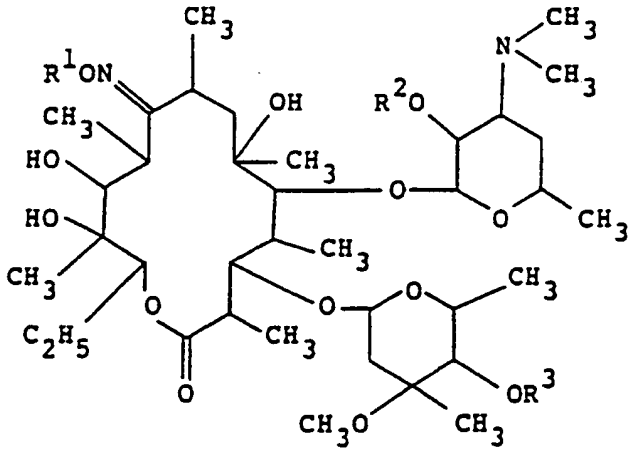
wobei R^1 eine 2-Alkenylgruppe mit 3 bis 15 Kohlenstoffatomen ist oder eine Arylmethylgruppe, ausgewählt aus der Gruppe der Benzyl-, Benzhydryl-, Trityl- und Naphthylmethylgruppen, oder eine Arylmethylgruppe ist, substituiert durch 1 bis 3 Vertreter, die unter einem Halogenatom, einer Alkylgruppe mit 1 bis 4 Kohlenstoffatomen, einer Alkoxygruppe mit 1 bis 4 Kohlenstoffatomen, einer Nitrogruppe und einer Alkoxycarbonylgruppe mit 2 bis 6 Kohlenstoffatomen ausgewählt werden; R^2 ist eine substituierte Silylgruppe der Formel $SiR^4R^5R^6$ (wobei R^4, R^5 und R^6 gleich oder verschieden voneinander sind und jeweils ein Wasserstoffatom, eine Alkylgruppe mit 1 bis 15 Kohlenstoffatomen, eine phenylsubstituierte Alkylgruppe, bei welcher die Alkyleinheit 1 bis 3 Kohlenstoffatome hat, eine Phenylgruppe, eine Cycloalkylgruppe mit 5 bis 7 Kohlenstoffatomen, oder eine Alkenylgruppe mit 2 bis 5 Kohlenstoffatomen darstellen, wobei mindestens einer von R^4, R^5 und R^6 verschieden von einem Wasserstoffatom ist) und R^3 stellt ein Wasserstoffatom oder R^2 dar.

3. Verfahren zur Herstellung eines 6-O-Methylerythromycin A-Derivates, dargestellt durch die allgemeine Formel



wobei R^1 eine 2-Alkenylgruppe mit 3 bis 15 Kohlenstoffatomen ist, oder eine Arylmethylgruppe, die aus Benzyl-, Benzhydryl-, Trityl- und Naphthylmethylgruppen ausgewählt ist, oder die Arylmethylgruppe, substituiert durch 1 bis 3 Vertreter, welche unabhängig voneinander unter einem Halogenatom, einer Alkoxygruppe mit 1 bis 4 Kohlenstoffatomen, einer Nitrogruppe und einer Alkoxycarbonylgruppe mit 2 bis 6 Kohlenstoffatomen ausgewählt werden; R^2 ist eine substituierte Silylgruppe der Formel $SiR^4R^5R^6$ (wobei R^4, R^5 und R^6 gleich oder verschieden voneinander sind und jeweils ein Wasserstoffatom, eine Alkylgruppe mit 1 bis 15 Kohlenstoffatomen, eine phenylsubstituierte Alkylgruppe, in welcher die Alkyleinheit 1 bis 3 Kohlenstoffatome hat, eine Phenylgruppe, eine Cycloalkylgruppe mit 5 bis 7 Kohlenstoffatomen, oder eine Alkenylgruppe mit 2 bis 5 Kohlenstoffatomen, darstellt, wobei mindestens einer von R^4, R^5 und R^6 verschieden von einem Wasserstoffatom ist) und R^3 stellt ein Wasserstoffatom oder R^2 dar,

umfassend, dass man in jeder gewünschten Reihenfolge Erythromycin A-9-oxim mit einer Verbindung der Formel R^1-X (wobei R^1 wie oben definiert ist und X ein Halogenatom ist) und mit einem substituierten Silylierungsmittel, beinhaltend eine Gruppe R^2, umsetzt, wodurch eine Verbindung, dargestellt durch die allgemeine Formel



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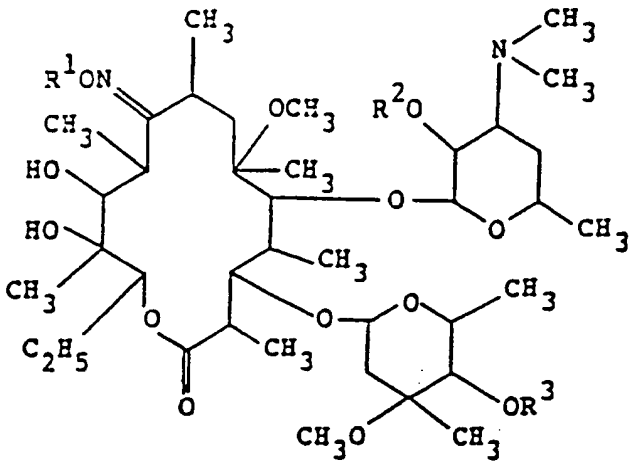
entsteht (wobei R^1, R^2 und R^3 wie oben definiert sind), und dann die resultierende Verbindung mit einem Methylierungsmittel umsetzt.

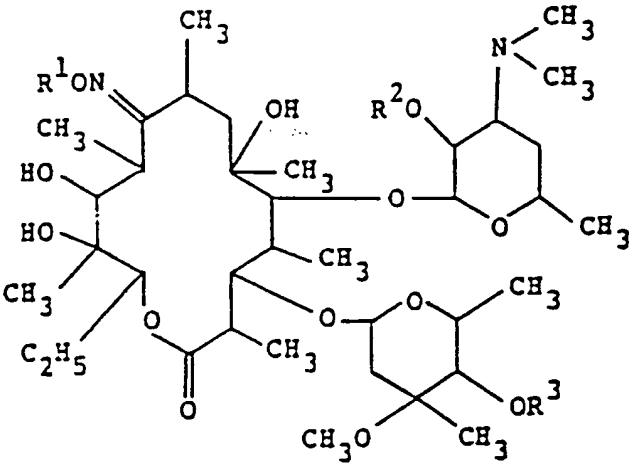
Revendications

1. Dérivé de la 6-O-méthylérythromycine A représentée par la formule générale



dans laquelle R^1 est un groupe 2-alcényle en C_3-C_{15}, un groupe arylméthyle choisi parmi les groupes benzyle, benzhydryle, trityle et naphthyl-méthyle ou ce groupe arylméthyle substitué par 1 à 3 membres choisis indépendamment les uns des autres parmi un atome d'halogène, un groupe alcoxy en C_1-C_4, un groupe nitro et un groupe alcoxycarbonyle en C_2 à C_6, R^2 est un groupe silyle substitué répondant à la formule $-SiR^4R^5R^6$ (dans laquelle R^4, R^5 et R^6 sont identiques ou différents et sont chacun un atome d'hydrogène, un groupe alkyle en C_1 et C_{15}, un groupe alkyle substitué par un groupe phényle dans lequel la partie alkyle est en C_1-C_3, un groupe phényle, un groupe cycloalkyle en C_5 à C_7 ou un groupe alcényle en C_2 à C_5, sous réserve qu'au moins un des symboles R^4, R^5 et R^6 est autre qu'un atome d'hydrogène) et R^3 est un atome d'hydrogène ou R^2.

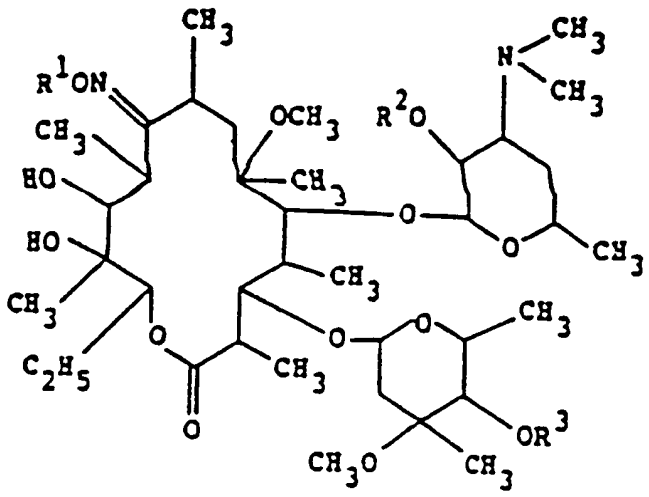
2. Dérivé de l'érythromycine A représentée par la formule générale



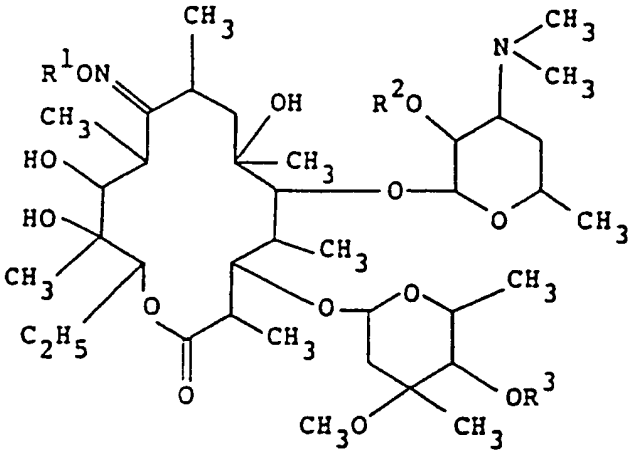
dans laquelle R^1 est un groupe 2-alcényle en C_3-C_{15}, un groupe arylméthyle choisi parmi les groupes benzyle, benzhydryle, trityle et naphthyl-méthyle ou ce groupe arylméthyle substitué par 1 à 3 éléments choisis parmi un atome d'halogène, un groupe alkyle en C_1-C_4, un groupe alcoxy en C_1 à C_4, un groupe nitro et un groupe alcoxycarbonyle en C_2 à C_6, R^2 est un groupe silyle substitué répondant à la formule $-SiR^4R^5R^6$ (dans laquelle R^4, R^5 et R^6 sont identiques ou différents et sont chacun un atome d'hydrogène, un groupe alkyle en C_1-C_{15}, un groupe alkyle substitué par un groupe phényle dans lequel la partie alkyle est en C_1-C_3, un groupe phényle, un groupe cycloalkyle en C_5 à C_7 ou un groupe alcényle en C_2 à C_5, sous réserve qu'au moins un des symboles R^4, R^5 et R^6 est autre qu'un

atome d'hydrogène) et R^3 est un atome d'hydrogène ou R^2.

3. Procédé de préparation d'un dérivé de la 6-O-méthylérythromycine A représentée par la formule générale



dans laquelle R^1 est un groupe 2-alcényle en C_3 à C_{15}, un groupe arylméthyle choisi parmi les groupes benzyle, benzhydryle, trityle et naphthyl-méthyle, ou ce groupe arylméthyle substitué par 1 à 3 éléments choisis indépendamment les uns des autres parmi un atome d'halogène, un groupe alcoxy en C_1-C_4, un groupe nitro et un groupe alcoxycarbonyle en C_2 à C_6, R^2 est un groupe silyle substitué répondant à la formule $-SiR^4R^5R^6$ (dans laquelle R^4, R^5 et R^6 sont identiques ou différents et sont chacun un atome d'hydrogène, un groupe alkyle en C_1-C_{15}, un groupe alkyle substitué par un groupe phényle dans lequel la partie alkyle est en C_1-C_3, un groupe phényle, un groupe cycloalkyle en C_5 à C_7 ou un groupe alcényle en C_2 à C_5, sous réserve qu'au moins un des symboles R^4, R^5 et R^6 est autre qu'un atome d'hydrogène) et R^3 est un atome d'hydrogène ou R^2 qui comprend le fait de réagir, dans n'importe quel ordre désiré, l'érythromycine A 9-oxime avec un composé répondant à la formule R^1-X (dans laquelle R^1 est tel que défini ci-dessus et X est un atome d'halogène) et avec un agent de silylation substitué ayant un groupe R^2 pour donner un composé représenté par la formule générale



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dans laquelle R^1, R^2 et R^3 sont tels que définis ci-dessus), puis le fait de faire réagir le composé obtenu avec un agent de méthylation.